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Topiramate, zonisamide and small for gestational age: maternal factors, timing of exposure and baby fat

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Topiramate, Zonisamide and Small For Gestational Age: Maternal Factors, Timing of Exposure and Baby Fat

Association Between Topiramate and Zonisamide Use During Pregnancy and Low Birth Weight.

Hernández-Díaz S, Mittendorf R, Smith CR, Hauser WA, Yerby M, Holmes LB; for the North American Antiepileptic Drug Pregnancy Registry. *Obstet Gynecol* 2014;123:21–28.

The recent article from the North American Antiepileptic Drug Pregnancy Registry (NAAEDPR) presents data showing that babies exposed in utero to topiramate (TPM) and zonisamide (ZNS) have a significantly lower birth weight and shorter length than babies exposed to lamotrigine (LTG) or a control group. This difference, of a mean of 200 grams in weight and 1 cm in length, when controlled for gestational age, contributed to a higher than expected proportion of babies who were small for gestational age (SGA) occurring in the TPM and ZNS groups.

Commentary

Small for gestational age (SGA) is commonly defined as weight below the 10th percentile for gestational age (1). The concern regarding SGA is its implications for development; it is associated with an increased risk for neonatal distress, permanent deficits in growth and neurocognitive development, and mortality. However, SGA babies are a heterogeneous group, and approximately 50% are constitutionally small, due to maternal ethnicity, body habitus, and body mass index (BMI) and these infants will develop normally (2). In 2005, 10% of births to Hispanic, American Indian/Alaska Native, and non-Hispanic white women in the United States met the criteria for SGA, and the occurrence in non-Hispanic Black births was 17% (1).

Topiramate is associated with an increased risk of major congenital malformations (MCMs), with 1.4 % of births showing facial clefts, recently described by this group (3, 4) and others (5). These rare cases were excluded from the analysis herein. Within the North American Antiepileptic Drug Pregnancy Registry (NAAEDPR), a structurally related drug, zonisamide has been associated with a low risk of MCMs, with none occurring in 90 monotherapy exposures, therefore the upper limit of the 95% confidence interval (CI) is 3.3% (3).

The authors adjusted for many factors that could contribute to small for gestational age, including smoking, maternal illness, and socioeconomic indicators. The overwhelming majority of mothers were Caucasian (> 85%) which minimizes the ethnic variability that could result in some SGA babies. This was also very highly educated cohort. Having at least 2 years of college education was reported in 45% of the topiramate-treated mothers, and this was the least educated group.

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The investigators also evaluated factors that would not be predicted to associate with SGA, but need to be looked at just the same, such as the indication for use including migraine and epilepsy. They found no association by indication. Overall, this appears to be a group with low risk for ethnic or socioeconomic influences on the occurrence of SGA. Therefore these rates may be underestimates for other populations.

An epilepsy-related factor that associates with SGA is the occurrence of seizures during pregnancy (6). This was evaluated and showed no association.

Another epilepsy-related factor associated with SGA is AED polytherapy (7). The authors evaluated a group exposed to lamotrigine plus other AEDs and found an SGA proportion of 10%, lower than that with topiramate or zonisamide polytherapy. Polytherapy exposures, although incompletely described in this report and not discussed as independent groups, showed a trend toward an adverse effect. From the spectrum of AED associations with SGA, TPM as monotherapy or polytherapy carried the most risk.

The question as to the underlying mechanism of topiramate-associated SGA is paramount. Weight loss surely does occur with these AEDs, and TPM is now marketed as part of a combination pharmaceutical agent having an indication for the treatment of severe obesity (8). An obvious limitation of this study is that maternal weight and maternal weight change during pregnancy were not adjusted for in this analysis, since they are associated with either SGA or LGA (large for gestational age) (9). It was stated, however, that the data was not available for such.

Topiramate's mechanism of action in producing weight loss may be primarily through the hypothalamus, affecting both the sense of satiety mediated in the ventromedial hypothalamus and hunger recognition mediated in the lateral hypothalamus. Decreased gastric motility has also been proposed as a contributing mechanism, controlled in the dorsomedial

hypothalamic nucleus. One recent report (10) supports this hypothesis; in a study of 40 migraine patients treated with topiramate 100 mg/day for three months, a significant reduction in body fat occurred, without a change in the resting metabolic rate (RMR), pointing toward a hypothalamic mechanism .

There was no dose effect found, but there was a profound timing effect. The proportion of SGA in offspring whose mothers stopped topiramate monotherapy before the third trimester was quite low at 7.3%, while for those who continued it throughout the third trimester, the rate was highest at 19.6%. This difference was not significant, likely due to small numbers (not given), but the trend is interesting, as is the trend polytherapy on increasing the rates of SGA especially with topiramate use.

The third trimester is the period of gestation when most fetal body fat is deposited. At 20-weeks gestation, fat comprises 0.5% of the fetal body, after which the amount increases, reaching 7.8% at the 34-weeks gestation, and 16% before birth. Nearly 500 g of fetal body fat are acquired in the last trimester of pregnancy and during the last month of intrauterine life the fetus gains as much as 14 g of fat per day (11). Does topiramate minimize fetal body fat deposition, as suggested by timing of an adverse effect in correlation with fetal growth patterns?

This information, while incomplete and difficult to explain since fetuses don't eat and we do not have information on maternal weight gain, deserves consideration when counseling women with epilepsy and migraine who take these medications. These mothers may need to consciously override their hypothalamically-mediated behavior and eat more!

by Cynthia L. Harden, M.D.

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